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Request for Grant of a Patent

The Patent Office
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1. Your reference — MCG/P76519 GB

2. Patent Application number *(the Patent Office will fill in this part)* — 23 SEP 1998 — **9820746.7**

3. Full name, address and postcode of the or of each Applicant *(underline all surnames)*

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THE PATENT OFFICE
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23 SEP 1998
LONDON

7518483001

Patents ADP Number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation — ENGLAND

4. Title of the Invention — MICRONISED PHARMACEUTICAL COMPOSITIONS

5. Name of your Agent *(if you have one)* — **URQUHART-DYKES & LORD**

"Address for Service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

91 Wimpole Street
London
W1M 8AH
Great Britain

Patents ADP Number *(if you know it)* — 1644002

6. If you are declaring priority from one or more earlier Patent Applications, give the country and the date of filing of the or of each of these earlier Applications and *(if you know it)* the or each Application Number

Country	*Priority application No. (if you know it)*	*Date of Filing (Day/month/year*

7. If this Application is divided or otherwise derived from an earlier UK Application, give the Number and the Filing Date of the earlier Application

Number of earlier application	*Date of Filing (Day/month/year)*

8. Is a Statement of Inventorship and of Right to Grant of a Patent required in support of this request ? *(Answer 'Yes' if:*

a) any Applicant named in part 3 is not an inventor, or
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11. I/We request the grant of a Patent on the basis of this Application

Signature Date 23 September 1998

URQUHART-DYKES & LORD

12. Name and daytime telephone number of person to contact in the United Kingdom

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MICRONISED PHARMACEUTICAL COMPOSITIONS

The present application relates to improvements in or relating to pharmaceutical compositions comprising micronised colistin sulphomethate sodium.

Background and Prior Art

Colistin is an anti-bacterial cationic cyclic polypeptide belonging to the polymixin group. It is produced as a secondary metabolite of *Bacillus polymyxa* var. *colistinus*. Treatment of colistin base with formaldehyde and sodium bisulphite results in the production of colistin sulphomethate sodium. This is described in Japanese patent 4898/1957. The product is a crystalline powder which is soluble in water.

Colistin is of particular benefit in the treatment of serious infections caused by bacterial pathogens such as *Pseudomonas aeruginosa*, *Escherichia coli* and *Klebsiella sp.* An important property of colistin is that bacteria which are sensitive to the drug do not readily acquire resistance. Colistin as a pharmaceutical may be prepared into numerous different preparations, e.g. topical, bladder irrigation, oral such as tablets, or as intravenous or intra-muscular injections.

Colistin sulphate can be prepared from colistin. It is currently used to treat gram negative infections of the body such as intestinal infections due to various micro-organisms and, usually in association with other antibiotics, for the suppression of bowel flora.

Colistin sulphomethate sodium can also be prepared. It exists as a white to slightly yellow hygroscopic powder. It is commercially supplied at a particle size of 100-200 μm mass median diameter. The powder is highly soluble in water and as such is used for parenteral administration. As a powder, colistin sulphomethate sodium must be stored in air-tight containers, preferably protected from the light. Colistin sulphomethate sodium is used in the treatment of injections in patients suffering from cystic fibrosis, a genetic disease which affects many body systems, and which develops at a young age. Various glands of the body do not function properly. The disease is marked by a malfunction of the glands in the lining of the bronchial tubes. Instead of producing their normal thin mucus, the bronchial glands produce a thick, sticky mucus that stagnates in the tubes. Microbes are able to multiply readily, causing serious respiratory infections ultimately leading to respiratory failure. It is known that colistin sulphomethate sodium is effective in treatment of infections caused by these microbes e.g. *Pseudomonas aeruginosa*. The usual form of administration is as a solution for inhalation after nebulisation. The nebulised solution is prepared by taking a vial in which there is a known dosage of colistin sulphomethate sodium powder, injecting water into the vial and then inhaling the solution into the lungs through a nebuliser.

Whilst jet nebulisation therapy has been shown to be successful, the nebulisation technique has several drawbacks. Jet nebulisers utilise compressed gases (usually air) to convert a drug solution into a spray. The compressed air passes through a narrow venturi orifice and negative pressure is created. Liquid is drawn from a fluid reservoir through a

feed tube, fragments into droplets, and is accelerated to a velocity sufficient for more than 99% of the droplet mass to impact on baffles or on the nebuliser where droplets coalesce and drain back into the fluid reservoir. Only 1% of the aerosol mass leaves the nebuliser directly. The outgoing air becomes saturated with water derived from liquid retained in the nebuliser, and this has two important consequences: Firstly, the nebuliser is cooled and reaches an equilibrium temperature approximately 10°C below ambient, so that the patient inhales a relatively cold spray. Secondly, the evaporation of water causes the concentration of solutes to increase with time.

There are many different designs of nebuliser available which use different flow rates of compressed gas. The output from these nebulisers will all be different and accordingly it is difficult for a patient to ensure that a constant dose is administered. The nebulisers themselves are bulky due to the compressors which are required. Although described as being transportable, the nebuliser/compressor system is not truly portable. When they are undergoing treatment, patients need to remain connected to the mouthpiece of the nebuliser for approximately 20 minutes in order to complete the therapy and in order to ensure that the correct dose is administered. An electrical supply is needed to run the nebuliser.

It will be seen from the above that, although colistin sulphomethate sodium is a valuable pharmaceutical in the treatment of infections occurring during cystic fibrosis and other bacterial infections, there are a number of disadvantages which mean that it is not widely accepted as a treatment

regime, particularly for infants. It has been determined that many of the problems arise from the preferred delivery method described above, i.e. as a nebulised liquid.

Summary of Invention

It has now been discovered that micronised colistin sulphomethate sodium can be administered to the airways of a patient using a powder dose inhalation device. The micronised colistin may be used alone or with a carrier, such as lactose.

According to the present invention, there is firstly provided the use of micronised colistin sulphomethate sodium in a method of treatment of the human body, particularly in the treatment of bacterial infections of the pulmonary system, most particularly in the treatment of secondary infections in patients suffering from cystic fibrosis, by powder inhalation.

According to a further aspect of the present application, there is provided a pharmaceutical composition comprising micronised colistin sulphomethate sodium and a carrier, in the absence of free liquid.

According to a yet further aspect of the present invention, there is provided a pharmaceutical dosage form suitable for use with a dry powder inhaler comprising micronised colistin sulphomethate sodium, optionally together with a carrier, and a container. The container is preferably a capsule.

Detailed Description

Micronised colistin sulphomethate sodium may be defined as being a powder wherein at least 90% by volume of the powder

comprises particles have a diameter of less than 10 micrometers. Most preferably, at least 50% of the particles have a diameter of less than 8 micrometers. More preferably, at least 25% of the particles have a diameters of less than 6 micrometers.

Figure 1 shows a particle size analysis of micronised colistin.

Medicaments for administration by inhalation should be of a controlled particle size in order to achieve maximum penetration into the lungs, a suitable particle size range being 0.01-10, usually 1-8 micrometers. Particle sizes may be measured by a number of methods, e.g. by laser diffraction or microscope analysis.

Micronised colistin sulphomethate sodium may be prepared by fluid energy milling, ball milling, spray drying or precipitation. The colistin sulphomethate sodium may be administered in conjunction with a carrier. The carrier may be any non-toxic material which is chemically inert to the colistin sulphomethate sodium and will be acceptable for inhalation or for administration. Examples of carriers which may be used include inorganic salts, e.g. sodium chloride or calcium carbonate; organic salts, e.g. sodium tartrate or calcium lactate; organic compounds, e.g. urea; monosaccharides, e.g. lactose, arabinose or dextrose; disaccharides, e.g. maltose or sucrose; polysaccharides, e.g. starches and dextrans. A particularly preferred carrier is a lactose, e.g. crystalline lactose.

The present invention also provides a method for preparing a composition of the invention which comprises mixing together micronised colistin sulphomethate sodium and a carrier. The colistin sulphomethate sodium and the carrier may be blended in a drum, hoop or Y-cone blender as known in the art.

The carrier does not have to have the same particle size specification as the colistin sulphomethate sodium. The carrier may in fact generally be of a larger particle size than that of the colistin sulphomethate sodium in order to facilitate delivery from the inhalation device and yet not be deposited in the finer airways of the lungs. The inclusion of a carrier may ease dosage of pharmaceutical and carrier into capsules. Preferably at least 50%, and more desirably at least 70% by volume of the carrier particles have an effective particle size in the range of 30 to 150, especially 30 to 80, micrometers. The admixture of pharmaceutical and carrier may contain up to 75% by weight, more preferably up to 50% by weight of carrier. Generally the ratio of colistin sulphomethate sodium will be in the range of 5:1 to 1:2 preferably 4:1 to 1:1 by weight.

It has been surprisingly found that water absorption of a micronised powder is comparatively low, e.g. approximately 5-7% by weight under normal atmospheric conditions. It has also been found that the micronised powder does not stick together. In powders having a larger particle size, the particles can stick together because of static forces. However, this is not found in the colistin sulphomethate sodium of the present invention. This is a further surprising advantage of the present application.,

In addition to the micronised colistin sulphomethate sodium and, optionally, the carrier, the composition may contain other ingredients, such as colouring matter or flavouring agents such as saccharine, which may be present in inhalant compositions. Antistatic agents may also be added, e.g. as described in GB-A-2269992 (Rhone-Poulenc Rorer Ltd). It is preferred to use the minimum of such other ingredients.

The powder formulation may contain other pharmaceutical ingredients such as bronchodilators. Such other pharmaceutical ingredients preferably have an effective particle size similar to that of the colistin.

The micronised powder may be delivered to the lungs through a specialised powder inhalation device. Most preferred is location of the powdered pharmaceutical within a hard capsule or a blister package. The capsule or blister is ruptured or broached within the inhaler device, thereby enabling the powder to be inhaled through the mouthpiece as air is sucked in.

There is also provided, therefore, as a further feature of the invention, a dosage unit comprising a capsule containing colistin sulphomethate sodium, preferably in the form of a pharmaceutical composition of the present invention. The capsule may be formed of gelatin or a plastics material.

The amount of composition contained in the capsule will, of course, depend upon the desired dosage. However, the capsule suitably contains from 10 to 200 milligrams, most preferably 30 to 150 milligrams of the colistin sulphomethate sodium. The colistin sulphomethate sodium may be delivered with or without

a carrier. If a carrier is used then clearly a larger amount of the mix of carrier and pharmaceutical is required. It has been found that the capsule should contain a larger dose of drug than the amount which will actually be delivered to the lungs. Dosages are usually expressed in "units". 80 mg of colistin sulphomethate is equivalent to approximately 1 million units of colistin sulphomethate. One unit of colistin sulphomethate is contained in 0.00007874 mg of the first International Reference Preparation (1966) of colistin sulphomethate. Children with cystic fibrosis may be treated with nebulised colistin sulphomethate sodium at a level of 500,000 units, twice daily. The respirable fraction from a conventional nebuliser (CR 50 System 22) is approximately 9 mg of colistin sulphomethate sodium from a 500,000 unit dose. This can be tested using a multistage impinger and measuring mass collected at stages 3 and 4.

A preferred device for delivering the pharmaceutical composition in accordance with the present invention is the Aerohaler (Registered Trade Mark) from Boehringer Ingelheim. This device uses a hard gelatin capsule which is pierced by two metal needles in the side of a capsule. When the patient inhales through the mouthpiece, air enters the bottom of the chamber causing the capsule to spin and throw out its contents into the airstream. The unit holds six capsules in a carousel cartridge. When all six capsules have been used, the unit locks and it must be re-loaded. Another preferred device is the Turbospin (Registered Trade Mark) originating from PH & T. This device also uses a gelatin capsule which is pierced in the bottom by a single metal needle. When the patient inhales through the mouthpiece, air is drawn in through the

tangentially ranged slits around the chamber. This spins the capsule and throws out the contents into the airstream. A flip top on the device allows up to three spare capsules to be stored. Other devices known in the art for delivery of encapsulated powders by inhalation can be used.

The capsule keeps the powder dry and thus in flowable form. The capsules should preferably be designed to protect their contents from light, e.g. they should be opaque or the capsules may be packed and/or stored in opaque containers, e.g. coloured or covered containers, or metal foil.

The invention is further described by reference to the following Examples.

Examples

Example 1

Micronised colistin sulphomethate sodium was produced by fluidised energy milling using a Hosokawa Alpine mill of powdered colistin sulphomethate sodium having an average particle size of approximately 100 μm supplied by Dumex Pharmaceuticals. A sample of the micronised colistin sulphomethate sodium was suspended in chloroform and the particle size analysed by a laser counter. Figure 1 shows the range of particle sizes of the micronised colistin.

Example 2

Gelatin pharmaceutical capsules (standard size 2) were obtained from Shionogi Qualicaps. The capsules were filled using a standard dosator (Zanassi LZ64) under controlled temperature and humidity conditions (17°C/45% RH). Colistin sulphomethate

sodium was filled into the capsules either as pure micronised powder or together with a lactose carrier (lactose monohydrate lactochem pharmaceutical grade from Borculo Whey Products). The fills are as shown on Table 1.

TABLE 1

Run Number	Mix Used	Total Fill
1	Colistin	125 mg
2	Colistin/Lactose (1:1)	165 mg
3	Colistin/Lactose (2:1)	140 mg
4	Colistin/Lactose (4:1)	130 mg
5	Colistin	125 mg

When colistin sulphomethate sodium is used alone, it flows well. Filling weights are standard. If a mixture of colistin to lactose as in Run 2 is used then the mixed powder flows well through the machine but there is sticking of the components of the dosator. Sticking reduces in Runs 3 and 4. Tests found respirable fractions in the region of 16 to 20 mg. This is the mass of colistin sulphomethate sodium collected on stages 3 and 4 of the multistage liquid impinger and equates to particles having a size less than about 3 to 4 micrometers.

Example 3

Filled capsules produced from Runs 1 to 4 above were stored for nine months under various humidity conditions. There was no degradation or clumping of the colistin sulphomethate sodium.

There was no noticeable clumping of colistin sulphomethate sodium on the capsule walls.

CLAIMS

1. The use of micronised particles of colistin sulphomethate sodium wherein at least 90% by volume of the micronised particles have a diameter of less than 10 micrometers in the treatment of a pulmonary infections by powder inhalation.

2. The use of colistin sulphomethate sodium as claimed in Claim 1 wherein the micronised powder is mixed with a carrier.

3. The use of colistin sulphomethate sodium as claimed in Claim 2 wherein the carrier is lactose.

4. A composition comprising micronised colistin sulphomethate sodium as defined in Claim 1 and a carrier, in the absence of free liquid.

5. A composition as claimed in Claim 4 wherein the carrier is lactose.

6. A composition as claimed in Claim 4 or Claim 5 wherein the ratio of colistin sulphomethate sodium to carrier is from 5:1 to 1:2 by weight.

7. A composition as claimed in Claim 4 or Claim 5 wherein the ratio of colistin sulphomethate sodium to carrier is from 4:1 to 1:1 by weight.

8. The composition as claimed in any one of Claims 4 to 7 wherein at least 50% by volume of the carrier particles have an effective particle size in the range of 30-150 micrometers.

9. A composition as claimed in any one of Claims 4 to 8 wherein at least 50% by volume of the micronised colistin sulphomethate sodium has a particle diameter of less than 8 micrometers.

10. A composition as claimed in any one of Claims 4 to 9 wherein at least 25% of the particles of micronised colistin sulphomethate sodium have a diameter of less than 6 micrometers.

11. A composition as claimed in any one of Claims 4 to 10 wherein the micronised colistin sulphomethate sodium is prepared in the desired particle size range using a fluid energy mill.

12. A process for the preparation of a composition as claimed in any one of Claims 4 to 11 which comprises mixing micronised colistin sulphomethate sodium and a carrier.

13. A pharmaceutical dosage form suitable for use with a dry powder inhaler comprising micronised colistin sulphomethate sodium wherein at least 90% by volume of the particles have a diameter less than 10 micrometers or a composition according to any one of Claims 4 to 11 and a container.

14. A pharmaceutical dosage form according to Claim 13 wherein the container is a hard gelatin capsule.

15. A capsule containing micronised colistin sulphomethate sodium wherein at least 90% by volume of the micronised particles have a diameter of less than 10 micrometers.

16. A capsule as claimed in Claim 15 containing from 10 to 200 micrograms of micronised colistin sulphomethate sodium.

17. A capsule as claimed in Claim 15 containing from 30 to 100 micrograms of micronised colistin sulphomethate sodium.

18. A capsule as claimed in any one of Claims 15 to 17 further comprising a carrier.

19. A capsule as claimed in Claim 18 when the carrier is lactose.

20. A capsule according to any one of Claims 15 to 19 which is opaque.

21. A capsule according to any one of Claims 15 to 19 or a composition according to any one of Claims 4 to 11 packed in an opaque container.

22. A capsule containing micronised colistin sulphomethate sodium when the micronised particles have a diameter of less than 10 micrometers, in unit dosage form.

23. A composition substantially as herein described with reference to the accompanying drawings.

24. A pharmaceutical dosage form substantially as herein described with reference to the accompanying drawings.

25. A capsule substantially as herein described with reference to the accompanying drawings.

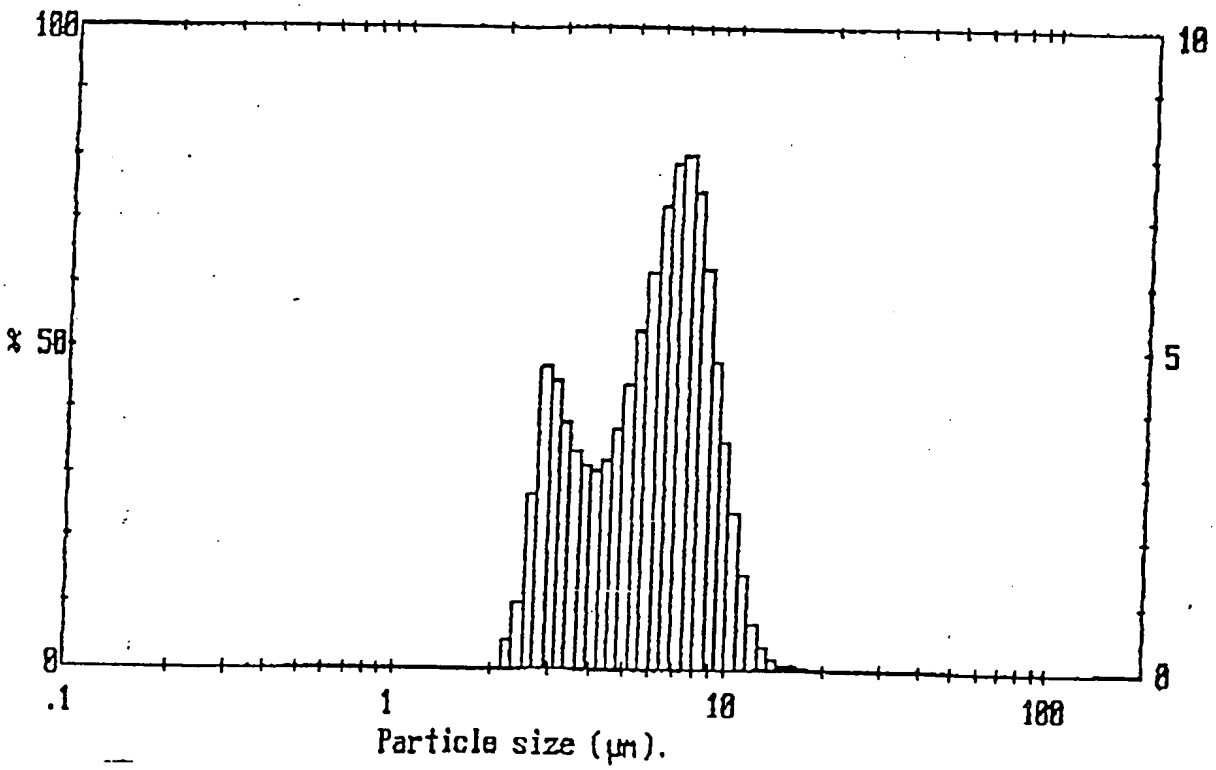
26. A process for the preparation of a composition as claimed in Claim 12 and substantially as herein described.

ABSTRACT

MICRONISED PHARMACEUTICAL COMPOSITIONS

Pharmaceutical compositions are described comprising micronised colistin sulphomethate sodium. The micronised pharmaceutical may be used together with a carrier such as lactose. The pharmaceutical compositions may be packed into containers such as gelatin capsules and administered by powder inhalation.

FIGURE 1



Particle sizing of micronised colistin sulphomethate sodium.